Original Investigation

Use of Plant-Based Therapies and Menopausal Symptoms
A Systematic Review and Meta-analysis

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IMPORTANCE Between 40% and 50% of women in Western countries use complementary therapies to manage menopausal symptoms.

OBJECTIVE To determine the association of plant-based therapies with menopausal symptoms, including hot flashes, night sweats, and vaginal dryness.

DATA SOURCES The electronic databases Ovid MEDLINE, EMBASE, and Cochrane Central were systematically searched to identify eligible studies published before March 27, 2016. Reference lists of the included studies were searched for further identification of relevant studies.

STUDY SELECTION Randomized clinical trials that assessed plant-based therapies and the presence of hot flashes, night sweats, and vaginal dryness.

DATA EXTRACTION Data were extracted by 2 independent reviewers using a predesigned data collection form.

MAIN OUTCOMES AND MEASURES Hot flashes, night sweats, and vaginal dryness.

RESULTS In total, 62 studies were identified, including 6653 individual women. Use of phytoestrogens was associated with a decrease in the number of daily hot flashes (pooled mean difference of changes, −1.31 [95% CI, −2.02 to −0.61]) and vaginal dryness score (pooled mean difference of changes, −0.31 [95% CI, −0.52 to −0.10]) between the treatment groups but not in the number of night sweats (pooled mean difference of changes, −2.14 [95% CI, −5.57 to 1.29]). Individual phytoestrogen interventions such as dietary and supplemental soy isoflavones were associated with improvement in daily hot flashes (pooled mean difference of changes, −0.79 [−1.35 to −0.23]) and vaginal dryness score (pooled mean difference of changes, −0.26 [−0.48 to −0.04]). Several herbal remedies, but not Chinese medicinal herbs, were associated with an overall decrease in the frequency of vasomotor symptoms. There was substantial heterogeneity in quality across the available studies, and 46 (74%) of the included randomized clinical trials demonstrated a high risk of bias within 3 or more areas of study quality.

CONCLUSIONS AND RELEVANCE This meta-analysis of clinical trials suggests that composite and specific phytoestrogen supplementations were associated with modest reductions in the frequency of hot flashes and vaginal dryness but no significant reduction in night sweats. However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.

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Menopause is considered the end of a woman's reproductive life, generally indicated by the time when menstrual periods stop permanently.[1] The menopausal transition and its associated changes vary widely.[2,3] Symptoms associated with menopause include hot flashes, night sweats, and vaginal dryness, with 50.3% to 82.1% of menopausal women reporting hot flashes or night sweats.[4,5] Medical treatments for these symptoms are available, including hormone replacement therapy. However, given the potentially negative health consequences of hormone replacement therapy on cardiovascular health and breast cancer,[6,7] 40% to 50% of women in Western countries choose to use complementary therapies, including plant-based therapies.[8,9]

A broad range of plant-based therapies may improve menopausal symptoms. These therapies include the oral use of phytoestrogens such as dietary soy isoflavones and soy extracts; herbal remedies such as red clover and black cohosh; and Chinese and other medicinal herbs. Although associations of these therapies with menopausal symptoms have been evaluated in randomized trials,[10,11] most of these studies were limited by inadequate power (ie, limited sample size), a short follow-up period, suboptimal quality (eg, high dropout rates), and inconsistent findings. Prior summaries of evidence are limited by a focus on a specific therapy (eg, phytoestrogens),[12] evaluation of a specific symptom (eg, hot flashes), and being nonquantitative[13] or largely nonsystematic[14] in nature. Therefore, an updated and comprehensive quantitative review is important, given the large number of plant-based therapies used by women to treat menopausal symptoms.

We conducted a systematic review and meta-analysis of intervention studies evaluating the association of plant-based therapies with menopausal symptoms.

Methods

Data Sources and Search Strategy

This review was conducted using a predefined protocol and in accordance with PRISMA and MOOSE guidelines.[15,16] Three electronic databases (Ovid MEDLINE, EMBASE, and Cochrane Central) were searched until March 27, 2016, without language restriction. The computer-based searches combined terms related to (1) the exposures (or interventions, where appropriate) such as herbal, phytoestrogens, soy, isoflavone, ginseng, black cohosh, *Cimicifuga*, ERr 731 rhubarb raponticin, St John's wort, complementary medicine, traditional medicine, and Chinese medicine; (2) menopausal symptoms (eg, hot flashes, night sweats, vasomotor symptoms, vaginal dryness, menopause); (3) study design (eg, clinical trials, randomized clinical trials); and (4) relevant population (eg, humans) (eAppendix 1 in the Supplement). Two independent reviewers (T. V., S. K., and/or C. O.-W.) screened the titles and abstracts of all studies initially identified, according to the selection criteria. Any disagreement was resolved through consensus or consultation with a third independent reviewer (T. M.). Full texts were retrieved from studies that satisfied all selection criteria. Reference lists of selected studies and reviews identified on the topic were searched to identify additional publications.

Study Selection and Eligibility Criteria

Intervention studies were eligible if they were randomized clinical trials (RCTs); assessed effects of any plant-based therapy listed above in perimenopausal, menopausal, or postmenopausal women, compared with a placebo or no treatment; and collected end points for menopausal symptoms, including hot flashes, night sweats, and vaginal dryness. To maintain consistency and because of difficulty in interpreting results without a placebo or control, head-to-head trials without a placebo group that compared nonhormonal therapies with estrogen or with other medications were excluded. Study populations in the eligible trials included women experiencing menopausal symptoms recruited from health care settings or general populations. No restriction on length of follow-up was applied.

Data Extraction

The exposures or interventions eligible for inclusion in the current review were summarized using the following broad groupings: (1) biologically based therapies including phytoestrogens (dietary soy isoflavones and supplements and extracts of soy isoflavones, red clover isoflavones, and other phytoestrogens), black cohosh and other biologically based therapies such as flaxseed, St John's wort, wheat germ, and St John's wort with chaste tree; and (2) medicinal herbs, including Chinese medicinal herbs and other medicinal herbs such as ERr 731 rhubarb raponticin. Two authors (S. K., C. O.-W.) independently extracted data and a consensus was reached in case of any inconsistency with involvement of a third author (T. M.). A predesigned electronic data abstraction form was used to extract relevant information. In instances of multiple publications, the most up-to-date information was extracted.

Assessing the Risk of Bias

Two reviewers (S. K., T. M.) independently rated the quality of studies. The Cochrane Collaboration's tool[17] was used to assess the risk of bias. Detailed information on the assessment of study quality and risk of bias is provided in eAppendix 2 in the Supplement.

Statistical Analysis

Treatment effects were defined as the differences in outcomes between the treatment and placebo at the end of the trial. For continuous outcomes, summary measures were presented as mean differences. For data reported as medians, ranges, or 95% confidence intervals, we calculated means and standard deviations as previously described.[18] To enable a consistent approach to the meta-analysis and enhance interpretation of the findings, units of measurement were converted where appropriate. Most crossover trials in this review did not report adequate crossover analysis; therefore, we used data from the first period only.[19] The inverse variance weighted method was used to combine summary measures using random-effects models to minimize effects of

Table 1. Characteristics of the 62 Randomized Clinical Trials Included in the Systematic Review and Meta-analysis

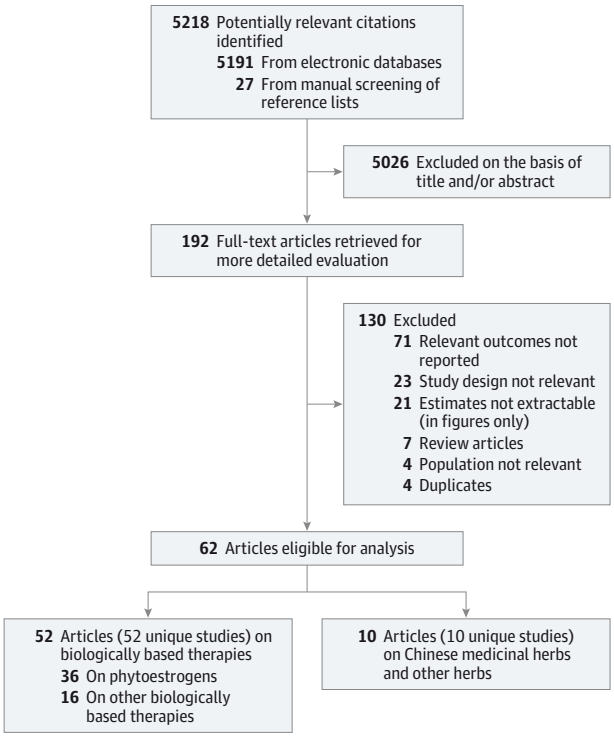
	Biologically Based Therapies[a]		
	Phytoestrogens (Soy Isoflavones, Red Clover Isoflavones, and Other Phytoestrogens)	Black Cohosh and Other Biologically Based Therapies	Medicinal Herbs: Chinese and Other Medicinal Herbs[b]
Eligible studies			
No. of unique studies	36[24-59]	16[19,60-74]	10[3,75-83]
Duration of follow-up, median (IQR), wk	12 (12-16)	12 (8-21)	12.0 (12-16)
Participants			
Total	3762	1654	1237
Median (IQR), No.	80 (51-157)	87 (52-123)	92 (64-110)
Age, median (IQR), y	53.5 (53.0-54.0)	52.0 (51.6-55.0)	52 (50-53)
Location			
Europe	15	2	4
North America	7	3	0
Asia-Pacific	7	4	6
South America	5	2	0
Middle East	2	5	0

Abbreviation: IQR, interquartile range.

[a] Biologically based therapies included phytoestrogens (dietary soy isoflavones and supplements and extracts of soy isoflavones, red clover isoflavones and other phytoestrogens), black cohosh and other biologically based therapies such as flaxseed, St John's wort, wheat germ, and St John's wort with chaste tree.

[b] Medicinal herbs included ERr731 rhubarb raponticin and Chinese or other medicinal herbs.

Figure 1. Literature Search for Identification of Randomized Clinical Trials on the Association Between Use of Plant-Based Therapies and Menopausal Symptoms



Sixty-two studies included in the current systematic review and meta-analysis are randomized clinical trials.

between-study heterogeneity.[20] We also conducted sensitivity analyses using fixed-effects models. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic and was distinguished as low (I^2 ≤25%), moderate (I^2 >25% and <75%), or high (I^2 ≥75%).[21] We evaluated publication bias using funnel plots and Egger regression symmetry tests.[22]

Sensitivity analyses were performed to assess the influence of each individual study, omitting the studies that had the largest effect on the overall result one by one. Furthermore, we restricted the analysis to studies that did not include participants with a history of breast cancer. Study-level characteristics including geographic location, duration of treatment, number of total participants, and risk of bias were prespecified as characteristics for assessment of heterogeneity and were evaluated using stratified analyses and random-effects meta-regression.[23] A narrative synthesis and construction of descriptive summary tables were performed for these studies that could not be quantitatively pooled.

All tests were 2-tailed; $P \leq .05$ was considered statistically significant. Stata release 13 (StataCorp) was used for all analyses.

Results

Study Identification and Selection

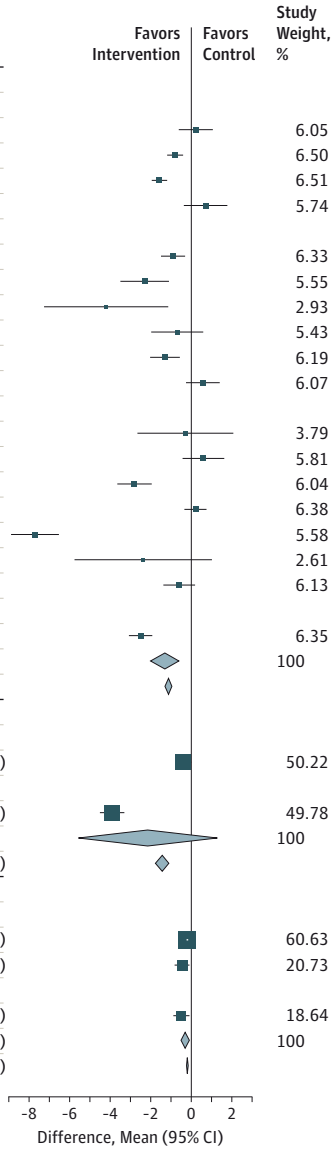
We identified 5218 relevant citations. After screening titles and abstracts, 192 articles were selected for detailed evaluation of their full texts. Of those, 62 articles, based on 62 unique RCTs, met our inclusion criteria and were included in the review: 52 unique studies about biologically based therapies (36 on phytoestrogens and 16 on black cohosh and other biologically based therapies) and 10 unique studies on medicinal herbs (**Table 1**, **Figure 1**; eAppendix 3 in the Supplement).

Characteristics of Included Studies

The 62 RCTs reported results for 6653 unique women (Table 1; eTables 1 and 2 in the Supplement). Twenty-one RCTs were based in Europe; 17 in Asia-Pacific; 10 in North America; 7 in South America; and 7 in the Middle East (Table 1). The baseline age of participants ranged from 18 to 75 years (eTables 1 and 2 in the Supplement). The duration of the interventions

Figure 2. Meta-analysis of Randomized Clinical Trials on the Associations Between Use of Phytoestrogen Supplementation and Menopausal Symptoms

Source	No. of Participants		Change, Mean (95% CI)[a]		Difference, Mean (95% CI)[b]	Study Weight, %
	Intervention	Control	Intervention	Control		
No. of Hot Flashes in 24 Hours						
Dietary soy isoflavones						
Lewis et al,[47] 2006	33	33	-0.71 (-3.79 to 2.37)	-0.93 (-4.67 to 2.81)	0.22 (-0.62 to 1.06)	6.05
Cheng et al,[33] 2007	30	30	-0.80 (-2.47 to 0.87)	0.0 (-1.37 to 1.37)	-0.80 (-1.19 to -0.41)	6.50
Albertazzi et al,[26] 1998	51	53	-5.01 NR	-3.42 NR	-1.59 (-1.95 to -1.20)	6.51
Van Patten et al,[59] 2002	78	79	-1.8 (-7.01 to 3.41)	-2.5 (-10.4 to 5.40)	0.70 (-0.37 to 1.77)	5.74
Supplements and extracts of soy isoflavones						
Aso et al,[28] 2012	77	83	-1.9 (-5.43 to 1.63)	-1 (-4.92 to 2.92)	-0.90 (-1.49 to -0.31)	6.33
Nahas et al,[51] 2007	40	40	-6.5 (-11.4 to -1.64)	-4.2 (-10.0 to 1.60)	-2.30 (-3.50 to -1.10)	5.55
Faure et al,[39] 2002	39	36	-6.4 (-18.6 to 5.83)	-2.2 (-16.3 to 11.9)	-4.20 (-7.26 to -1.14)	2.93
Penotti et al,[52] 2003	28	34	-5.3 (-10.6 to 0.01)	-4.6 (-9.30 to 0.10)	-0.70 (-1.98 to 0.58)	5.43
Ferrari et al,[40] 2009	85	95	-3.7 (-8.8 to 1.40)	-2.4 (-7.01 to 2.21)	-1.30 (-2.03 to -0.57)	6.19
Hachul et al,[41] 2011	19	19	-4.33 (-6.92 to -1.74)	-4.9 (-7.41 to -2.39)	0.57 (-0.26 to 1.40)	6.07
Red clover						
Knight et al,[44] 1999	13	12	-3.1 (-9.27 to 3.07)	-2.8 (-8.44 to 2.84)	-0.30 (-2.66 to 2.06)	3.79
Baber et al,[30] 1999	25	26	-1.18 (-4.98 to 2.62)	-1.77 (-5.26 to 1.72)	0.59 (-0.43 to 1.61)	5.81
Jeri et al,[43] 2002	30	30	-3.4 (-6.97 to 0.17)	-0.60 (-3.58 to 2.38)	-2.80 (-3.65 to -1.95)	6.04
Atkinson et al,[29] 2004	102	103	-0.8 (-4.92 to 3.32)	-1.0 (-4.53 to 2.53)	0.20 (-0.34 to 0.74)	6.38
Lipovac et al,[24] 2012	50	59	-8.6 (-14.3 to -2.92)	-0.9 (-7.51 to 5.71)	-7.70 (-8.88 to -6.52)	5.58
van de Weijer et al,[58] 2002	16	14	-2.08 (-8.14 to 3.98)	0.29 (-11.0 to 11.6)	-2.37 (-5.75 to 1.01)	2.61
Tice et al,[56] 2003	84	85	-3.4 (-9.20 to 2.40)	-2.8 (-7.05 to 1.45)	-0.60 (-1.38 to 0.18)	6.13
Other phytoestrogens						
Dánna et al,[36] 2007	198	191	-2.5 (-8.09 to 3.09)	0.0 (-5.68 to 5.68)	2.50 (-3.07 to -1.93)	6.35
Random effects					-1.31 (-2.02 to -0.61)	100
Fixed effects					-1.12 (-1.29 to -0.95)	
No. of Night Sweats in 24 Hours						
Dietary soy isoflavones						
Cheng et al,[33] 2007	30	30	-0.60 (-2.21 to 1.01)	-0.20 (-1.63 to 1.23)	-0.40 (-0.79 to -0.01)	50.22
Red clover						
Lipovac et al,[24] 2012	50	59	-3.9 (-6.84 to -0.96)	0.0 (-3.37 to 3.37)	-3.90 (-4.50 to -3.30)	49.78
Random effects					-2.14 (-5.57 to 1.29)	100
Fixed effects					-1.44 (-1.77 to -1.11)	
Vaginal Dryness Score						
Supplements and extracts of soy isoflavones						
Kotsopoulos et al,[46] 2000	44	50	-0.35 (-0.59 to -0.11)	-0.15 (-0.35 to 0.05)	-0.20 (-0.24 to -0.16)	60.63
Colacurci et al,[34] 2004	15	15	-0.54 (-1.48 to 0.40)	-0.08 (-1.16 to 1.00)	-0.46 (-0.83 to -0.09)	20.73
Other phytoestrogens						
Brzezinski et al,[31] 1997	78	36	-0.93 (-3.03 to 1.17)	-0.44 (-2.34 to 1.46)	-0.49 (-0.89 to -0.09)	18.64
Random effects					-0.31 (-0.51 to -0.10)	100
Fixed effects					-0.21 (-0.25 to -0.17)	



Phytoestrogens are defined as use of dietary soy isoflavones and supplements and extracts of soy isoflavones, red clover isoflavones, and other phytoestrogens. Sizes of data markers are proportional to the inverse of the variance of the effect estimate. Vaginal dryness score was based on a 4-point scale of severity: 0 = nonexistent, 1 = mild, 2 = moderate, 3 = severe. Assessment of heterogeneity: number of hot flashes in 24 hours, I^2 = 94% (95% CI, 92%-98%; P < .001); number of night sweats in 24 hours, I^2 = 99% (95% CI, 98%-99%; P < .001); vaginal dryness score, I^2 = 48% (95% CI, 0%-85%; P = .15). NR indicates not reported.

[a] Mean change in outcome from randomization to the end of study.

[b] Mean difference of changes between treatment groups.

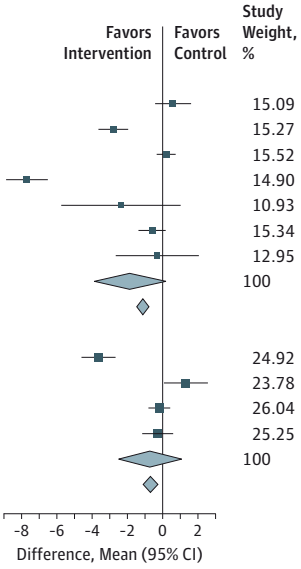
ranged from 4 weeks to 2 years, but the majority (28 studies) had a 12-week intervention period (Table 1; eTables 1 and 2 in the Supplement).

Biologically Based Therapies and Menopausal Outcomes

Thirty-six RCTs examined the association between any phytoestrogen use and menopausal symptoms (eTable 1 and eTable 3 in the Supplement). Because of differences in the outcomes assessed (eg, frequency of hot flashes, duration of hot flashes, or use of vasomotor symptom scores), 15 RCTs were not included in the meta-analysis. Therefore, data from 21 RCTs contributed to the meta-analysis, which showed an association of overall phytoestrogen use with a decrease in the number of daily hot flashes (pooled mean difference of changes between treatment groups, −1.31 [95% CI, −2.02 to −0.61]) and in vaginal dryness scores (pooled mean difference of changes between treatment groups, −0.31 [95% CI, −0.52 to −0.10]) (**Figure 2**; eTable 4 in the Supplement). The use of phytoestrogens was not associated with significant changes in 24-hour night sweat (pooled

Figure 3. Meta-analysis of Randomized Clinical Trials Assessing the Associations Between Use of Red Clover and Black Cohosh and Number of Daily Hot Flashes

Source	Plant-Based Therapy Dosage, mg	No. of Participants		Change, Mean (95% CI)[a]		Difference, Mean (95% CI)[b]	Study Weight, %
		Intervention	Control	Intervention	Control		
Red Clover							
Baber et al,[30] 1999	40	25	26	-1.18 (-4.98 to 2.62)	-1.77 (-5.26 to 1.72)	0.59 (-0.43 to 1.61)	15.09
Jeri et al,[43] 2002	40	30	30	-3.4 (-6.97 to 0.17)	-0.60 (-3.58 to 2.38)	-2.80 (-3.65 to -1.95)	15.27
Atkinson et al,[29] 2004	40	102	103	-0.8 (-4.92 to 3.32)	-1.0 (-4.53 to 2.53)	0.20 (-0.34 to 0.74)	15.52
Lipovac et al,[24] 2012	80	50	59	-8.6 (-14.3 to -2.92)	-0.9 (-7.51 to 5.71)	-7.70 (-8.88 to -6.52)	14.90
van de Weijer et al,[58] 2002	80	16	14	-2.08 (-8.14 to 3.98)	0.29 (-11.0 to 11.6)	-2.37 (-5.75 to 1.01)	10.93
Tice et al,[56] 2003	82	84	85	-3.4 (-9.20 to 2.40)	-2.8 (-7.05 to 1.45)	-0.60 (-1.38 to 0.18)	15.34
Knight et al,[44] 1999	160	13	12	-3.1 (-9.27 to 3.07)	-2.8 (-8.44 to 2.84)	-0.30 (-2.66 to 2.06)	12.95
Random effects						-1.84 (-3.87 to 0.19)	100
Fixed effects						-1.12 (-1.46 to -0.77)	
Black Cohosh							
Shahnazi et al,[71] 2013	6.5	42	42	-4.6 (-3.65 to -3.25)	-1.19 (-2.74 to 0.36)	-3.64 (-4.61 to -2.67)	24.92
Pockaj et al,[70] 2006	40	66	65	NR	NR	1.32 (0.07 to 2.57)	23.78
Frei-Kleiner et al,[68] 2005	42	81	41	1.66 (-1.65 to 4.97)	1.85 (-1.33 to 5.03)	-0.19 (-0.81 to 0.43)	26.04
Newton et al,[19] 2006	160	80	84	NR	NR	-0.28 (-1.16 to 0.60)	25.25
Random effects						-0.71 (-2.51 to 1.08)	100
Fixed effects						-0.69 (-1.12 to -0.27)	



Assessment of heterogeneity: red clover and number of hot flashes in 24 hours, I^2 = 97% (95% CI, 95%-98%; P < .001); black cohosh and number of hot flashes: I^2 = 60% (95% CI, 0%-89%; P = .08). Sizes of data markers are proportional to the inverse of the variance of the effect estimate. NR indicates not reported.

[a] Mean change in the number of hot flashes in 24 hours from randomization to the end of study.

[b] Mean difference of changes in the number of hot flashes in 24 hours between treatment groups.

mean difference of changes, −2.14 [95% CI, −5.57 to 1.29]) (Figure 2; eTable 4 in the Supplement). Study-specific estimates from studies (n = 15) not included in the meta-analyses generally supported an association of phytoestrogen use with a decrease in the frequency of individual menopausal symptoms, particularly in the number of hot flashes within 24 hours (eTable 5 in the Supplement).

Separate meta-analyses were performed for different types of interventions, including evaluation of overall soy isoflavones (dietary, supplements, and extracts) (12 studies), dietary soy isoflavones (4 studies), supplements and extracts of soy isoflavones (8 studies), and red clover isoflavones (7 studies) (**Figure 3**; eFigures 1, 2, and 3 in the Supplement). The results of the analyses restricted to any (dietary, supplemental, and extracts) soy isoflavone use or to supplements and extracts of soy isoflavones or solely to dietary soy isoflavones in general replicated the findings of the larger combined analyses on daily hot flashes and vaginal dryness scores (eFigures 1, 2, and 3 in the Supplement). Because of the limited number of studies, it was not possible to perform separate meta-analysis for the association between different types of phytoestrogen interventions and number of night sweats in 24 hours. There was no association between red clover and number of hot flashes in 24 hours (Figure 3). One study examined the association between red clover use and night sweats within 24 hours and showed a decrease in frequency of night sweats (mean difference of changes within 24 hours, −3.90 [95% CI, −4.50 to −3.30]).[24]

The association of black cohosh with menopausal symptoms was assessed in 9 RCTs. Data from 5 RCTs could not be included in the meta-analysis because those studies either assessed the association of black cohosh with different vasomotor symptoms scores or used black cohosh combined with other therapies. Therefore, data from only 4 RCTs contributed to the meta-analysis. Overall, black cohosh was not associated with changes in the number of hot flashes (pooled mean difference of changes within 24 hours, −0.71 [95% CI, −2.51 to 1.08]) (Figure 3; eTable 5 in the Supplement). Only 1 study assessed the association of black cohosh with the number of night sweats within 24 hours; this study reported no difference (mean difference of changes, 0.08 [95% CI, −0.30 to 0.47]).[19] Of the studies of black cohosh that could not be included in the meta-analysis, one study reported no difference in vasomotor symptoms score,[60] and 1 study reported a decrease in vasomotor symptoms score.[61] Two other studies that combined black cohosh with other therapies also reported a decrease in vasomotor symptom score[62,63] (eTable 6 in the Supplement). Also, 1 study showed a decrease in vaginal dryness score with the use of black cohosh (eTable 6 in the Supplement).[25] Seven additional studies of other biologically based therapies were identified and are summarized in eTable 6 in the Supplement. Four studies found an association with a decrease in symptoms with therapies including evening primrose, flaxseed, St John's wort, and combined therapies, whereas 3 studies of wheat germ, flaxseed, and St John's wort with chaste tree found no difference (eTable 6 in the Supplement).

Medicinal Herbs and Menopausal Symptoms

Because of the limited number of studies, it was not possible to perform meta-analysis on the associations of Chinese medicinal herbs and non-Chinese medicinal herbs with menopausal symptoms. The results of the RCTs for the association between use of Chinese medicinal herbs and menopausal symptoms were not consistent but in general showed no association (eTable 7 in the Supplement). One RCT[3] that used non-Chinese medicinal herbs reported a decrease in the number of hot flashes within 24 hours (mean difference of changes, −1.62 [95% CI, −2.29 to −0.95]) (eTable 7 in the Supplement). The beneficial association of non-Chinese medicinal herbs on menopausal symptoms was further supported by the studies that examined their association with weekly vasomotor symptoms score or hot flashes score (eTable 7 in the Supplement).

Sensitivity Analyses and Assessments of Bias, Study Quality, and Heterogeneity

For pooled analyses involving 5 or more studies, exclusion of any single study at one time from the meta-analysis or exclusion of trials that included participants with a history of breast cancer yielded results that were not substantially different. For 18 trials assessing the association of phytoestrogen supplementation with daily hot flashes, the mean differences ranged from −0.90 (95% CI, −1.44 to −0.37) to −1.43 (95% CI, −2.15 to −0.71) on exclusion of any single study at one time (eFigure 4 in the Supplement). The combined mean difference on excluding studies with participants with a history of breast cancer was −2.50 (95% CI, −3.07 to −1.93) (eFigure 5 in the Supplement). For 7 trials assessing the influence of red clover supplementation on daily hot flashes, the mean differences ranged from −0.75 (95% CI, −1.95 to 0.45) to −2.28 (95% CI, −4.61 to 0.06) when any single study was individually excluded (eFigure 6 in the Supplement).

Six RCTs showed high risk of bias in 1 domain, 10 in 2 domains, and 14 in 3 domains; the remaining RCTs showed high risk of bias in 4 or more domains (eTable 8 in the Supplement). However, most of the RCTs (n = 60) could not be clearly classified in 1 or more domains (eTable 8 in the Supplement). Seven of 12 analyses showed high between-study heterogeneity, with an I^2 estimate exceeding 75% ($P < .01$ for the Cochrane χ^2 statistic) (Figure 2 and Figure 3; eFigures 1, 2, and 3 in the Supplement). This level of heterogeneity could be explained by differences between studies attributable to heterogeneous study populations, methods, and effect estimates (eTable 8 in the Supplement).

Furthermore, for trials assessing the influence of phytoestrogen supplementation on the number of daily hot flashes, the identified heterogeneity was largely explained by the level of risk of bias (**Table 2**). The stratified analysis by the level of risk of bias showed that the association was stronger for studies that were classified with high risk of bias in 3 or more domains (Table 2). For trials examining the association between red clover supplementation and the number of hot flashes in 24 hours, heterogeneity was not explained by any of the study-level characteristics assessed (Table 2). Owing to a limited number of studies in the other meta-analysis, it was not possible to identify the factors contributing to the observed heterogeneity. Publication bias was assessed visually using Begg funnel plots for meta-analyses that included 5 or more studies. On examination, the plot was approximately symmetrical for the meta-analysis of phytoestrogen and number of hot flashes within 24 hours as well as for the meta-analysis of dietary and supplemental soy isoflavones and number of daily hot flashes (eFigure 7 in the Supplement). The plot for the analysis of the association of red clover with number of hot flashes within 24 hours was asymmetrical (eFigure 7 in the Supplement). The Egger test estimates were nonsignificant ($P > .05$) for all analyses that involved a minimum of 5 studies (eFigure 7 in the Supplement).

Discussion

In this systematic review and meta-analysis, some plant-based therapies were associated with modest reductions in the frequency of menopausal symptoms in women. Composite phytoestrogen supplementation and individual phytoestrogen interventions, such as dietary and supplemental soy isoflavones, were associated with improvement in some menopausal symptoms, including modest reductions in hot flashes and vaginal dryness but no significant reduction in night sweats. Additionally, several medicinal herbs were associated with improved menopausal symptoms. There was substantial diversity among the available studies in scientific rigor and quality.

Composite phytoestrogen supplementation was associated with improved menopausal symptoms. Our findings are further supported by other RCTs showing a beneficial association of phytoestrogen supplementation with the Kupperman Index, a scale commonly used in clinical practice to assess the severity of menopausal symptoms.[24,84,85] Our sensitivity analyses differentiating the association between overall phytoestrogen use and menopausal symptoms by type of phytoestrogen intervention (eg, whole foods, soy protein, and isoflavone extract supplementation groups) yielded broadly similar results. Supplementing with red clover, a rich source of phytoestrogens formononetin, biochanin A, daidzein, and genistein,[86] was associated with improvements in night sweats but not with the frequency of hot flashes.

There may be a plausible biological argument for these associations of phytoestrogens with improved symptoms. The 2 major subtypes of phytoestrogen, isoflavones and lignans, have a chemical structure similar to that of estradiol (ie, a form of estrogen) and therefore also appear to have estrogen-like properties. However, this mechanism of action also could be associated with adverse effects such as endometrial hyperplasia.[87]

There was no significant association between black cohosh (*Cimicifuga racemosa* or *Actaea racemosa*) supplementation and menopausal symptoms. Also, RCTs examining the association of black cohosh with menopausal scores, such as the Kupperman Index, have shown no beneficial association.[88]

Table 2. Pooled Mean Difference in the Number of Hot Flashes in 24 Hours by Subgroups of Randomized Clinical Trials Defined by Characteristic of Study Participants and Study Design

Subgroups by Study Characteristics	No. Studies	No. Intervention Group	No. Control Group	Difference, Mean (95% CI)[a]	*P* Value for Heterogeneity[b]
Association Between Use of Phytoestrogens and Number of Hot Flashes in 24 h, by Study-Level Characteristics[c]					
Location					
Europe	9	599	615	−2.16 (−3.25 to 1.07)	.09
North America	3	195	197	0.05 (−0.69 to 0.79)	
South America	3	89	89	−1.50 (−3.75 to 0.75)	
Asia-Pacific	3	115	121	−0.25 (−1.38 to 0.89)	
Duration of treatment, wk					
≤12	8	489	486	−1.26 (−2.39 to −0.13)	.87
>12	10	509	536	−1.38 (−2.35 to −0.40)	
No. of participants					
≥100	8	725	748	−1.67 (−2.81 to −0.52)	.38
<100	10	273	274	−0.94 (−1.78 to −0.11)	
Risk of bias[d]					
High	3	155	176	−3.09 (−7.29 to 1.11)	.03
Low	15	843	846	−0.92 (−1.53 to −0.32)	
Association Between Use of Any Soy Isoflavones (Dietary, Supplementary, and Extracts) and Number of Hot Flashes in 24 h, by Study-Level Characteristics[e]					
Location					
Europe	5	431	439	−1.53 (−2.18 to −0.89)	.06
North America	2	111	112	0.41 (−0.26 to 1.07)	
South America	2	59	59	−0.83 (−3.64 to 1.98)	
Asia-Pacific	1	77	83	−0.90 (−1.49 to −0.31)	
Duration of treatment, wk					
≤12	5	357	353	−1.26 (−2.63 to 0.10)	.63
>12	5	321	340	−0.90 (−1.46 to −0.33)	
No. of participants					
≥100	4	489	501	−1.21 (−1.98 to −0.43)	.44
<100	6	189	192	−0.77 (−1.64 to 0.10)	
Risk of bias					
High	2	105	117	−0.87 (−1.40 to −0.33)	.80
Low	8	573	576	−1.03 (−1.75 to −0.31)	
Association Between Use of Red Clover and Number of Hot Flashes in 24 h, by Study-Level Characteristics					
Location					
Europe	3	168	176	−3.31 (−9.35 to −2.74)	.87
North America	1	84	85	0.60 (−1.38 to 0.18)	
South America	1	30	30	−2.80 (−3.65 to 1.95)	
Asia-Pacific	2	38	38	0.45 (−0.49 to 1.39)	
Duration of treatment, wk					
≤12	2	132	133	−1.28 (4.22 to 1.66)	.76
>12	5	188	196	−2.09 (−5.40 to 1.23)	
No. of participants					
≥100	3	236	247	−2.66 (−6.55 to −1.22)	.54
<100	4	84	82	−1.15 (−3.35 to −1.03)	

[a] Mean difference refers to mean difference of changes between treatment groups.

[b] *P* value for heterogeneity was evaluated using random-effects meta-regression.

[c] Use of phytoestrogens includes use of soy isoflavones (dietary, supplements and extracts), red clover, and other phytoestrogens.

[d] Studies that showed high risk of bias in 1 domain or none were included in the low risk of bias category; otherwise, they were included in the high risk of bias category.

[e] Use of dietary and supplementary soy isoflavones includes use of dietary soy isoflavones and supplements and extracts of soy isoflavones.

Although black cohosh remains a widely studied and popular herbal remedy, there has been lack of clarity regarding the identity of its active compounds and its mechanisms of action, as well as concerns about possible adverse effects.[89] Beyond these existing uncertainties, the lack of beneficial results in the current meta-analysis does not support the use of black cohosh to reduce menopausal symptoms. Also, our analyses involving trials of medicinal herbal remedies showed no overall association of Chinese medicinal herbs such as dong quai on menopausal symptoms. By contrast, trials that assessed newer herbal remedies such as ERr 731 (an extract isolated from *Rheum rhaponticum*), and pycnogenol (extract from pine bark), reported associations with improvements in the number of hot flashes in 24 hours. However, more trials are

needed to determine the efficacy of these products on menopausal symptoms, because the evidence remains limited.

This study has a number of limitations. First, it is possible that both measured and unmeasured publication bias can limit our overall findings. In this regard, although evaluations with the conventional funnel plots and Egger test estimates indicate minimal publication bias, these approaches are limited by a qualitative assessment reliant on visual inspection and the fact that the majority of these assessments were based on a limited number of studies (between 5 and 10). We cannot exclude the possibility of publication bias from underreporting of negative findings. Second, the quality of included studies was limited. Variation in study quality contributed to the heterogeneity of findings noted in several of the meta-analyses presented in our study. Other sources of heterogeneity are likely to include population differences, including ethnicity—a factor in the presence of menopausal symptoms[90,91]—and differing age ranges. Furthermore, the supplements used in the trials may vary in quality and composition (ie, how much of the active ingredient is actually provided by the supplement), which might have contributed to the heterogeneity in effects observed in our analyses. Third, the number of available studies in some analyses was small, precluding our ability to quantitatively investigate the sources of the observed heterogeneity. Varying degrees of outcome measures may have contributed to heterogeneity. Fourth, self-reported measures of vasomotor symptoms may be subject to memory and reporting bias. Future studies should assess vasomotor symptoms physiologically using, for example, an ambulatory hot flash monitor to measure skin conductance. Given these limitations, the results of this systematic review and meta-analysis should be interpreted with caution.

This review may have several implications. First, the findings reinforce that a number of plant-based therapies may be associated with improvements in both individual and collective menopausal symptoms. Second, findings underscore major research and knowledge gaps, both in potentially beneficial therapies and in outcomes assessed. For instance, although the majority of the available studies focus on hot flashes, which are the most common symptom of the menopausal transition, a few studies evaluated other menopausal symptoms (eg, night sweats). There were insufficient numbers of studies assessing herbal remedies. Third, this review underscores the lack of data on adverse effects associated with long-term use of plant-based therapies. Information on any detrimental health effects, typically available in long-term intervention studies, is essential, given their potential relevance to postmenopausal health.

Conclusions

This meta-analysis of clinical trials suggests that composite and specific phytoestrogen supplementations were associated with modest reductions in the frequency of hot flashes and vaginal dryness but no significant reduction in night sweats. However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.

ARTICLE INFORMATION

Author Contributions: Drs Kunutsor and Muka had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Chowdhury, Ms Troup, and Drs Oliver-Williams and Muka contributed equally.
Study concept and design: Franco, Chowdhury, Muka.
Acquisition, analysis, or interpretation of data: Franco, Voortman, Kunutsor, Kavousi, Oliver-Williams, Muka.
Drafting of the manuscript: Franco, Chowdhury, Troup, Kunutsor, Oliver-Williams, Muka.
Critical revision of the manuscript for important intellectual content: Franco, Chowdhury, Troup, Voortman, Kunutsor, Kavousi, Oliver-Williams, Muka.
Statistical analysis: Kunutsor, Muka.
Obtained funding: Franco.
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